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10/500,307	11/22/2004	Pieter Hendrik Pouwels	GRT/117-509	9841

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EXAMINER	
TONGUE, LAKIA J	
ART UNIT	PAPER NUMBER
1645	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/500,307	POUWELS ET AL.	
	Examiner	Art Unit	
	LAKIA J. TONGUE	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18 and 21-39* is/are pending in the application.

4a) Of the above claim(s) *9-18,21-32 and 35-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,33 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/15/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on November 15, 2007 is acknowledged. Claims 1-18 and 21-39 are pending. Claims 1 and 2 have been amended. Claims 9-18, 21-32 and 35-39 are withdrawn from consideration. Claims 1-8, 33 and 34 are currently under consideration.

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on November 15, 2007 is in compliance with the provisions of 37 CFR 1.97 and has been considered. An initialed copy is attached hereto.

Declaration

2. The declaration by Pieter Pouwels filed November 15, 2007 has been considered.

Rejections Withdrawn

3. In view of Applicant's argument that "pI" refers to the isoelectric point of a protein, the rejection of claim 6 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention is withdrawn.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. The rejection of claims 1-8, 33 and 34 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained for the reasons set forth in the previous office action.

Applicant argues that:

1) Applicant's have amended claims 1 to clarify that both the crystallization referred to is the ability to form a crystalline monolayer and the protein which is modified comes from a *Lactobacillus* bacterium.

2) Applicant's agree with the assessment of the invention, although the fact that the claims have been limited from any S-protein to that of *Lactobacillus* needs to be taken into account.

3) The ability to crystallize, as specified by the claims, refers to the ability of the monomeric modified S-proteins to spontaneously form a two-dimensional crystalline monolayer that, under natural circumstances, comprises the surface layer that envelopes the entire bacterial cell, which is outlined in the declaration provided by Professor Pouwels.

4) As amended, claim 1 is directed to an S-protein which originated from a *Lactobacillus*. Moreover, it appears that misinterpretation of the claims may have led

the Examiner to believe that the claims are unduly broad in contrast to the reality that the claims are tightly based around one specific type of bacterial protein from *Lactobacillus*.

5) The specification describes the nature and properties of the modified *Lactobacillus* S-proteins and how to determine whether or not a modified S-protein can form a crystalline monolayer as specified by the claims.

6) Nothing in Bowie et al. prevents the invention being put into practice.

Applicant's arguments have been fully considered and deemed non-persuasive.

The claimed invention is directed to a modified bacterial surface layer (S-layer) protein, the modification comprising the internal insertion of a heterologous polypeptide, wherein said modified protein is able to crystallize to form a crystalline monolayer and the unmodified protein is from a Gram positive bacterium.

With regard to Points 1, 2 and 4, contrary to Applicant's response, while claim 1 was amended to clarify that the crystallization referred to is the ability to form a crystalline monolayer, claim 1 was not amended to clarify that the protein which is modified comes from a *Lactobacillus* bacterium. In fact, the claims remain broad in that claim 1 is drawn to a modified bacterial surface layer (S-layer) protein, the modification comprising the internal insertion of a heterologous polypeptide, wherein said modified protein is able to crystallize to form a crystalline monolayer and the unmodified protein is from a **Gram positive bacterium**. The specification does not offer support for a modified bacterial surface protein with any internal insertion and any and all **Gram**

positive bacterium species, wherein the protein is able to crystallize to form a crystalline monolayer.

With regard to Point 3, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., The ability to crystallize refers to the ability of the monomeric modified S-proteins to spontaneously form a two-dimensional crystalline monolayer that, under natural circumstances, comprises the surface layer that envelopes the entire bacterial cell) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Moreover, the declaration submitted by Professor Pouwels has been considered but is not deemed persuasive. The claims are broadly drawn and the data disclosed in the Declaration is not commensurate in scope with the claimed invention.

With regard to Point 5, while the specification describes the nature and properties of the modified *Lactobacillus* S-proteins, the claims are drawn to a modified bacterial surface layer (S-layer) protein, the modification comprising any internal insertion of a heterologous polypeptide, wherein said modified protein is able to crystallize to form a crystalline monolayer and the unmodified protein is from any **Gram positive bacterium**.

With regard to Point 6, Bowie et al. was incorporated to demonstrate that inserting any internal insertion into a polypeptide will affect the proteins functional properties. In other words, any insertion as claimed does not ensure that a modified

bacterial surface layer protein will maintain its ability to crystallize to form a crystalline monolayer.

As previously presented, *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. Thus, Applicant assumes a certain burden in establishing that inventions involving physiological activity are enabled.

Factors to be considered in determining whether a disclosure would require undue experimentation have been reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CRFC1988). The Wands factors have been considered in the establishment of this scope of enablement rejection. These factors include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the

invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The instant claims are drawn to a modified bacterial surface layer protein, the modification comprising the internal insertion of a heterologous polypeptide, wherein said modified protein is able to crystallize.

Breadth of the claims: The claims encompass any and all bacterial surface layer proteins, comprising any internal insertion of any heterologous polypeptide, wherein said modified protein is able to crystallize.

Direction or guidance presented in the specification: The specification does not provide substantive evidence that the claimed composition is capable of crystallizing. The specification is silent with regard to which bacterial surface layer protein will crystallize when the modification comprises any internal insertion of a heterologous polypeptide. The specification lacks adequate guidance/direction to enable a skilled artisan to practice the claimed invention commensurate in scope with the claims. The amino acid sequence of a protein determines its structural and functional properties, predictability of which internal insertion will result in certain activity, which is very complex, is well outside the realm of routine experimentation. Accurate predictions of a protein's function from mere sequence data are limited, therefore, the general knowledge and skill in the art is not sufficient, and thus the specification needs to provide an enabling disclosure.

Lastly, Applicant has failed to "fully characterize" the polypeptide that are capable of crystallizing when any internal insertion of any heterologous polypeptide is made. The specification does not describe with any degree of specificity which bacterial surface layer protein is to be used or at what point the internal insertion of a heterologous polypeptide is to be made, such that the specification might reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Presence or absence of working examples: There are no working examples, provided to rectify the missing information in the instant specification pertaining to the claimed variant.

State of the prior art: Protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie et al. (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome. Bowie et al. further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (column 1, page 1306). Bowie et al. further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable

expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). Accordingly, it follows that the functional domains associated with a given function can only be identified empirically. This constitutes undue experimentation. Therefore, given the lack of success in the art, the lack of working examples commensurate in scope to the claimed invention and the unpredictability of the generation of protective immunity, the specification, as filed, does not provide enablement for immunogenic compositions capable of adjuvanting a specific immune response.

Quantity of experimentation necessary: The quantity of experimentation necessary would be undue as no relevant evidence has been made of record establishing the amount of experimentation necessary. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to make/use the claimed genus. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

Thus, for all these reasons, the specification is not considered to be enabling for one skilled in the art to make and use the claimed invention as the amount of experimentation required is undue, due to the broad scope of the claims, the lack of guidance and working examples provided in the specification and the high degree of unpredictability as evidence by the state of the prior art, attempting the construct and test variants of the claimed invention would constitute undue experimentation.

5. The rejection of claims 1-8, 33 and 34 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for the reasons set forth in the previous office action.

Applicant argues that:

1) S proteins from Lactobacillus bacteria represent a tightly defined group of proteins. The specific modified S proteins described in the specification do therefore provide a representative and adequate illustration of the invention. Furthermore, the specification describes the necessary tests to show that a given modified Lactobacillus S protein can form a crystalline mono- layer as specified by the claims as also discussed above.

2) The Example shows insertion of a heterologous peptide in five different locations that retain the ability to form a two-dimensional crystalline structure and hence fall within the defined group as indicated by the claims. These represent the "representative number of *Lactobacillus* S-proteins with inserted heterologous proteins that can still crystallize" referred to in the Official Action.

3) Because of the common properties of all *Lactobacillus* S-proteins, the specific examples of modified proteins described in the specification do provide adequate written description for the claims under consideration.

Applicant's arguments have been fully considered and deemed non-persuasive.

The claimed invention is directed to a modified bacterial surface layer (S-layer) protein, the modification comprising the internal insertion of a heterologous polypeptide,

wherein said modified protein is able to crystallize to form a crystalline monolayer and the unmodified protein is from a Gram-positive bacterium.

With regard to Point 1, while Applicant's arguments may be true, the claims particularly claim 1 is broadly drawn to a modified bacterial surface layer (S-layer) protein, the modification comprising any internal insertion of a heterologous polypeptide, wherein said modified protein is able to crystallize to form a crystalline monolayer and the unmodified protein is from any **Gram positive bacterium**. The specification does not offer support for a modified bacterial surface protein with any internal insertion and any and all **Gram positive bacterium** species, wherein the protein is able to crystallize to form a crystalline monolayer.

With regard to Point 2, while the Example may show insertion of a heterologous peptide in five different locations that retain the ability to form a two-dimensional crystalline structure the fact still remains that the claims are broadly drawn and encompass more than the 5 insertion locations as described in the specification. As it stands the claims are drawn to an undetermined number of insertion locations, which have not been described nor has it been shown that any and all insertions will result in a protein that is able to crystallize to form a crystalline monolayer.

Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie et al. (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-

dimensional structures that allows them to function, carry out the instructions of the genome. Bowie et al. further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (column 1, page 1306). Bowie et al. further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). Accordingly, it follows that the functional domains associated with a given function can only be identified empirically. This constitutes undue experimentation. Therefore, given the lack of success in the art, the lack of working examples commensurate in scope to the claimed invention and the unpredictability of the generation of protective immunity, the specification, as filed, does not provide enablement for immunogenic compositions capable of adjuvanting a specific immune response.

With regard to Point 3, while the specification describes the nature and properties of the modified *Lactobacillus* S-proteins, the claims are drawn to a modified bacterial surface layer (S-layer) protein, the modification comprising any internal insertion of a heterologous polypeptide, wherein said modified protein is able to crystallize to form a crystalline monolayer and the unmodified protein is from any **Gram positive bacterium**.

As previously presented, to fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus of polypeptides or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession of the claimed invention. In the instant case, to fulfill the written description requirement, a representative number of S-proteins with inserted heterologous proteins that can still crystallize need to be described. Specifically, the specification needs to provide guidance as to which heterologous peptides/proteins can be inserted at a given position within a given S-protein and not affect crystallization.

A representative number of species means that the species that are adequately described are representative of the entire genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, disclosure of drawings, or by disclosure of relevant identifying characteristics, for example, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the Applicant was in possession of the claimed genus.

Moreover, the skilled artisan cannot envision the detailed chemical structure of the claimed polypeptides. The claims encompass a genus of polypeptides which are not adequately described. The recitation of any modified bacterial surface layer protein (indicating any protein) comprising the internal insertion, which is non-specific, represents a partial structure and the genus as claimed is highly variable. The specification fails to provide any additional representative species of the claimed genus to show that Applicant was in possession of the claimed genus. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential ability to bind a specific biological agent. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

The University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404. 1405 held that: ...To fulfill the written description requirement, a patent specification must describe an invention and does so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines Inc. , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an Applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not

that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2datl966.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. The rejection of claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention is maintained for the reasons set forth in the previous office action.

Applicant argues that:

1) Those working in the field would be able to understand what is meant by the claims.

Applicant's arguments have been fully considered and deemed non-persuasive.

With regard to Point 1, while the terms "antigen causing or specific for a disease" are understood, one would not readily understand that the term antigen causing or specific for a disease refers to an antigen causing a disease is the one responsible for the development of an auto-immune disease or an antigen specific for a disease is representative of a pathogen responsible for a disease.

As previously presented, claim 7 is rendered vague and indefinite by the use of the phrase "antigen causing or specific for a disease". It is unclear what is meant by

said term, as it is not explicitly defined in the specification. What constitutes "antigen causing or specific for a disease"? As written, it is impossible to determine the metes and bounds of the claimed invention.

Conclusion

7. No claim is allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakia J. Tongue whose telephone number is 571-272-2921. The examiner can normally be reached on Monday-Friday 8-5:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon

Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LJT
2/11/08

/Robert A. Zeman/

for Lakia J. Tongue, Examiner of Art Unit 1645